PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 December 1999 (06.12.99)	
International application No. PCT/EP99/03604	**Applicant's or agent's file reference** 1931PTWO
International filing date (day/month/year) 25 May 1999 (25.05.99)	**Priority date** (day/month/year) 27 May 1998 (27.05.98)
Applicant PAVESIO, Alessandra et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   05 November 1999 (05.11.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

A. Karkachi

Telephone No.: (41-22) 338.83.38

CLAIMS

1. Use of at least one hyaluronic acid derivative processed in the form of a three-dimensional structure enclosing empty spaces formed by communicating pores and/or fine fibres or microfibres entangled together for the preparation of a biocompatible biomaterial for the regeneration of mammal tissue, characterised in that said biocompatible biomaterial is free from cellular components and/or products thereof.

2. The use according to claim 1, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

3. The use according to anyone of claims 1 and 2, wherein said hyaluronic acid derivative is selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) The sulphated derivatives or N-sulphated derivatives of hyaluronic acid .

4. The use according to claim 3, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree lower than 85% and processed in the form of non woven tissue.

5. The use according to claim 4, wherein said esterification degree is comprised between 40 and 85%.

6. The use according to anyone of claims 4, or 5, wherein said esterification

degree is comprised between 45 and 75%.

7. The use according to anyone of claims 4-6, wherein said esterification degree is comprised between 60 and 70%,

8. The use according to anyone of claims 3-7 wherein said partial ester is the hyaluronic partial ester with benzyl alcohol.

9. The use according anyone of claims 1-3, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B).

10. The use according to claim 9 for osteochondral regeneration.

11. The use according to anyone of claims 1-10 wherein said biocompatible biomaterial consists essentially of at least one of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

12. The use according to anyone of claims 1-10 wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

13. The use according to anyone of claims 1-12, wherein said biocompatible biomaterial further contains pharmaceutically or biologically active substances.

14. The use according to any one of claims 1-13 wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.

15. A method for regenerating in vivo mammal tissue comprising applying in vivo to the site requiring such a treatment a biocompatible biomaterial containing at least one hyaluronic acid derivative processed in the form of a three-dimensional structure enclosing hollow spaces formed by communicating pores and/or fine fibres or microfibres entangled together, wherein said biomaterial is free from cellular components and/or products thereof.

16. The method according to claim 15, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

17. The method according to claim 15, wherein said hyaluronic acid derivative is selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are

esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) The sulphated derivatives or N-sulphated derivatives.

18. The method according to claim 17, wherein said hyaluronic acid derivatives is a partial ester of hyaluronic acid of class (A) having an esterification degree lower than 85% and processed in the form of non woven tissue.

19. The method according to claim 17, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 40 and 85% and is processed in the form of non woven tissue.

20. The method according to claim 17, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 45 and 75% and is processed in the form of non woven tissue.

21. The method according to claim 17, wherein said hyaluronic acid derivatives is a partial esters of hyaluronic acid of class (A) having an esterification degree comprised between 60 and 70% and is processed in the form of non woven tissue.

22. The method according to claim 17, wherein said partial ester is a hyaluronic partial ester with benzyl alcohol.

23. The method according to claim 17, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B).

24. The method according to claim 17, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B), for osteochondral regeneration.

25. The method according to claim 15, wherein said biocompatible biomaterial consists essentially of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

26. The method according to claim 15, wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

27. The method according to claim 15, wherein said biocompatible material further contains pharmaceutically or biologically active substances.

28. The method according to claim 15, wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.

AMENDED CLAIMS

[received by the International Bureau on 2 November 1999 (02.11.99); original claims 1 and 3-28 replaced by new claims 1 and 3-23; remaining claim unchanged (4 pages)]

Use of at least one hyaluronic acid derivative selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) the sulphated derivatives or N-sulphated derivatives of hyaluronic acid,

said hyaluronic acid derivative being processed in the form of a three-dimensional structure enclosing empty spaces formed by communicating pores and/or fine fibres or microfibres entangled together for the preparation of a biocompatible biomaterial for the regeneration of mammal tissue, characterised in that:

i) said biocompatible biomaterial is free from cellular components and/or products thereof;

ii) when the hyaluronic acid derivative belongs to the aforementioned class (A) , and is processed in the form of a non woven tissue, it has an esterification degree lower than 85%

2. The use according to claim 1, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

3. The use according to claim 1, wherein said esterification degree is comprised between 40 and 85%.

4. The use according to anyone of claims 1, or 3, wherein said esterification degree is comprised between 45 and 75%.

5. The use according to anyone of claims 4-6, wherein said esterification degree is comprised between 60 and 70%,

6. The use according to anyone of claims 3-7 wherein said partial ester is the hyaluronic partial ester with benzyl alcohol.

7. The use according anyone of claims 1-2, wherein said hyaluronic acid derivative is an autocrosslinked ester of class (B).

8. The use according to claim 7 for osteochondral regeneration.

9. The use according to anyone of claims 1-8 wherein said biocompatible biomaterial consists essentially of at least one of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

10. The use according to anyone of claims 1-9 wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

11. The use according to anyone of claims 1-10, wherein said biocompatible biomaterial further contains pharmaceutically or biologically active substances.

12. The use according to any one of claims 1-11 wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.

13. A method for regenerating in vivo mammal tissue comprising applying in vivo to the site requiring such a treatment a biocompatible biomaterial containing at least one hyaluronic acid derivative selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series,

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the

carboxy groups are esterified with polyalcohols of th aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) The sulphated derivatives or N-sulphated derivatives

said hyaluronic acid derivative being processed in the form of a three-dimensional structure enclosing hollow spaces formed by communicating pores and/or fine fibres or microfibres entangled together, wherein:

i) said biomaterial is free from cellular components and/or products thereof,

ii) when said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) and is processed in the form of non woven tissue, has an esterification degree lower than 85%

14. The method according to claim 13, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

15. The method according to claim 13, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 40 and 85% and is processed in the form of non woven tissue.

15.The method according to claim 13, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 45 and 75% and is processed in the form of non woven tissue.

16.The method according to claim 13, wherein said hyaluronic acid derivatives is a partial esters of hyaluronic acid of class (A) having an esterification degree comprised between 60 and 70% and is processed in the form of non woven tissue.

17.The method according to claim 13, wherein said partial ester is a hyaluronic partial ester with benzyl alcohol.

18.The method according to claim 13, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B).

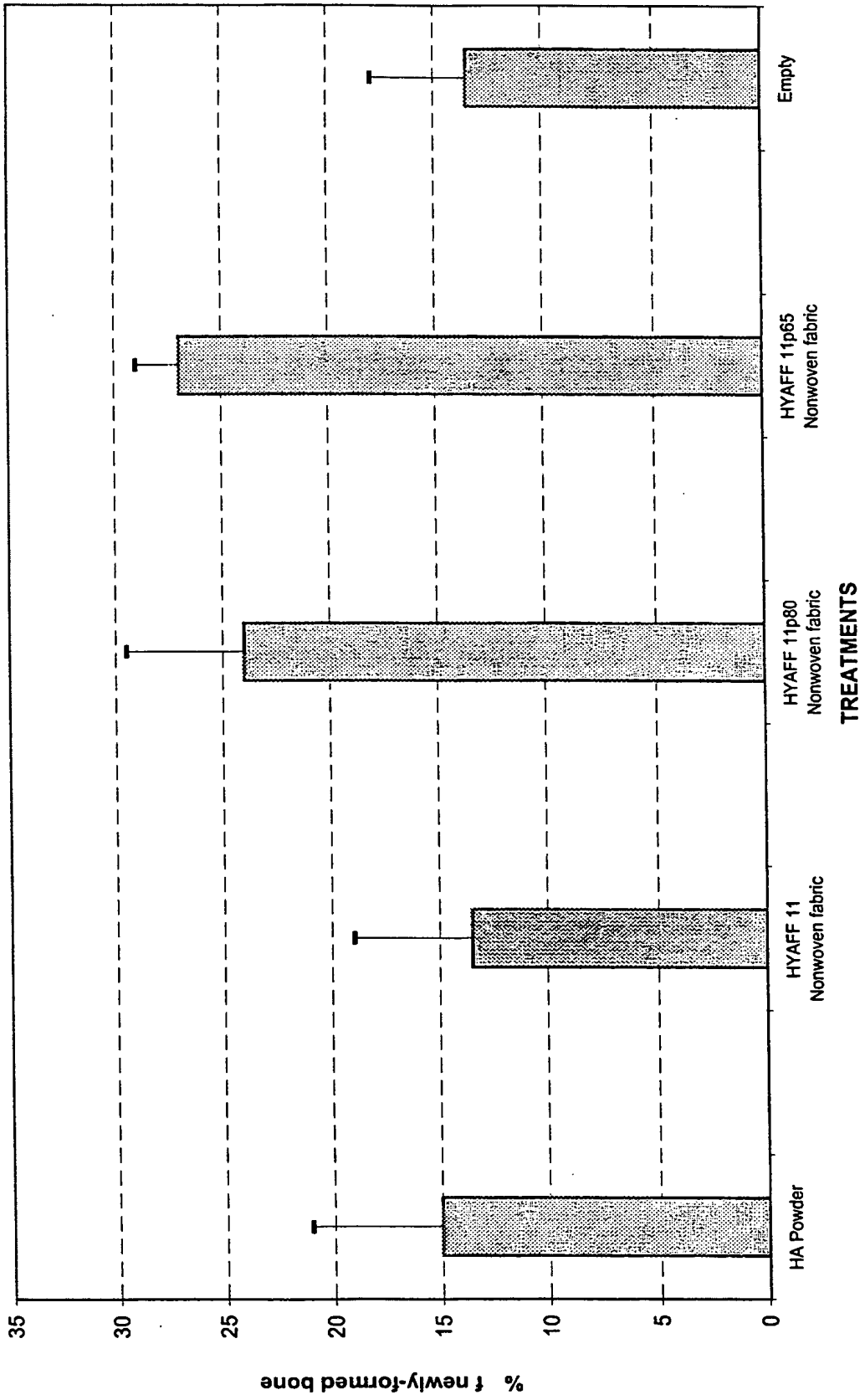
19.The method according to claim 13, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B), for osteochondral regeneration.

20. The method according to claim 13, wherein said biocompatible biomaterial consists essentially of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

21. The method according to claim 13, wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

22.The method according to claim 13, wherein said biocompatible material further contains pharmaceutically or biologically active substances.

23.The method according to claim 13, wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.


% f newly-formed bone
35
30
25
20
15
10
5
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HA Powder
HYAFF 11 Nonwoven fabric
HYAFF 11p80 Nonwoven fabric
HYAFF 11p65 Nonwoven fabric
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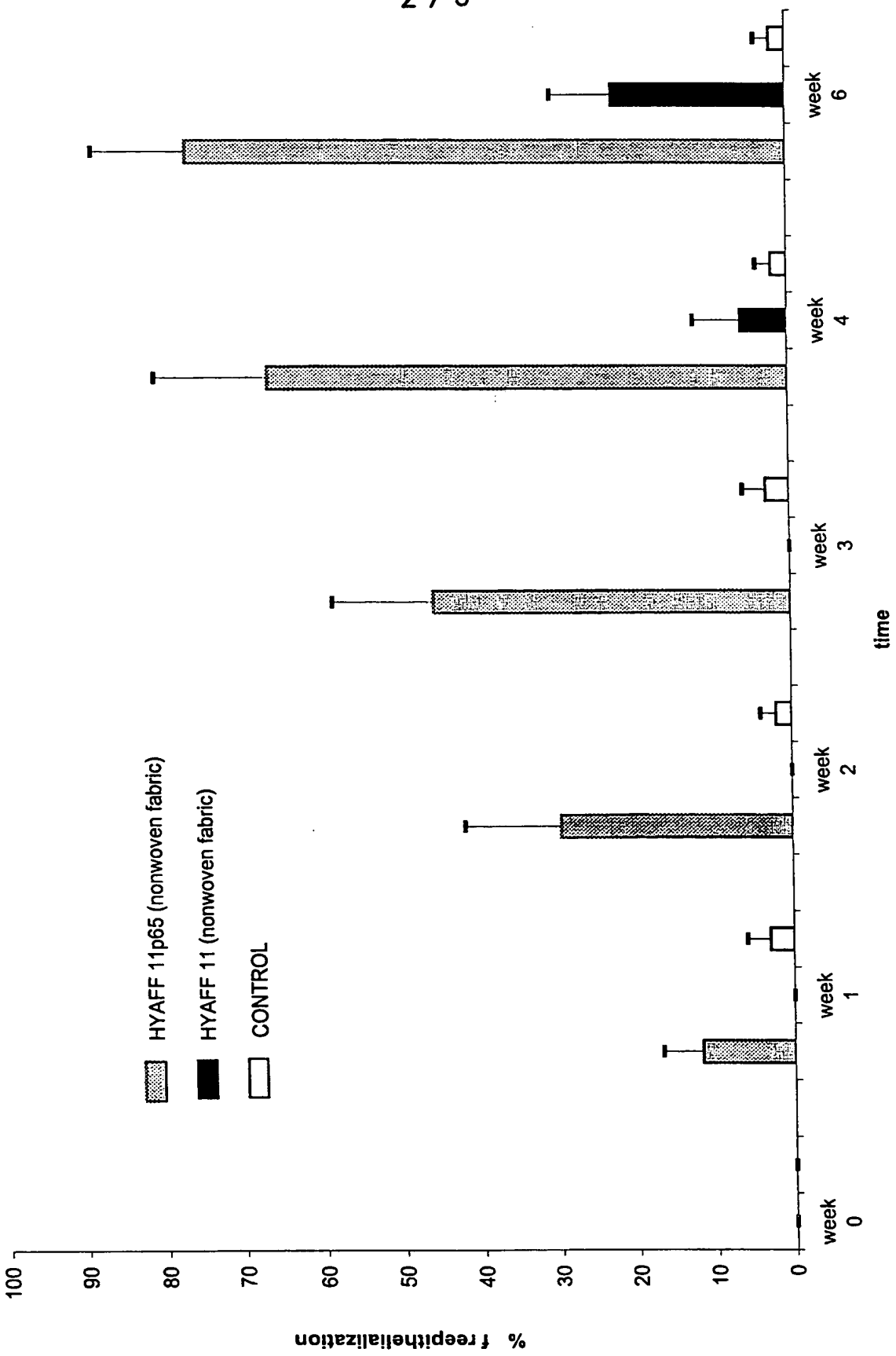
TREATMENTS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100
90
80
70
60
50
40
30
20
10
0
week 0
week 1
week 2
week 3
week 4
week 6
time
HYAFF 11p65 (nonwoven fabric)
HYAFF 11 (nonwoven fabric)
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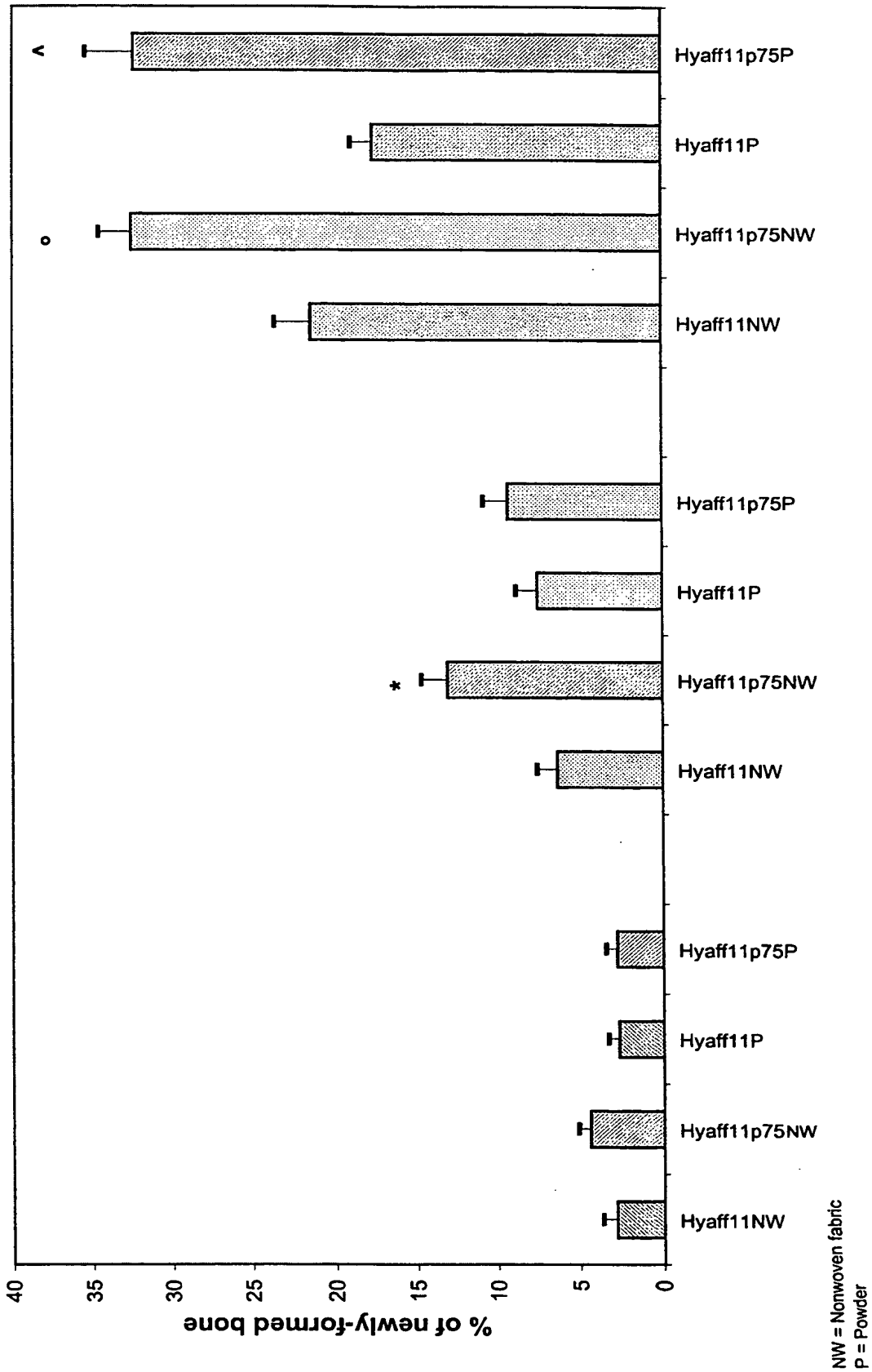
Hyaff11p75P
Hyaff11P
Hyaff11p75NW
Hyaff11NW
Hyaff11p75P
Hyaff11P
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Hyaff11NW
Hyaff11p75P
Hyaff11P
Hyaff11p75NW
Hyaff11NW
40
35
30
25
20
15
10
5
0
% of newly-formed bone
NW = Nonwoven fabric
P = Powder

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
1931PTWO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 03604	25/05/1999	27/05/1998
Applicant		
FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   BIOMATERIALS CONTAINING HYALURONIC ACID DERIVATIVES IN THE FORM OF THREE-DIMENSIONAL STRUCTURES FREE FROM CELLULAR COMPONENTS OR PRODUCTS THEREOF FOR THE IN VIVO REGENERATION OF TISSUE CELLS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03604

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61F2/28 D04H1/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61F D04H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LIN-SHU LIU: "An osteoconductive colagen/hyaluronate matrix for bone regeneration" BIOMATERIALS, vol. 20, 1999, pages 1097-1108, XP002112804 U.K. the whole document ---	1,2, 11-13, 15,16, 25-27
X	GLASS J. ET AL.: "A three-dimensional cell attachment matrix created by cross-linking RGD peptide modified hyaluronic acid" JOURNAL OF CELLULAR BIOCHEMISTRY, vol. Suppl.19a, 5 - 26 January 1995, page 178 XP002112805 abstract --- -/--	1,2, 11-13, 15,16, 25-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1999	03/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11803 A (M.U.R.S.T.) 24 June 1993 (1993-06-24) the whole document abstract	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/03604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311803 A	24-06-1993	IT 1254704 B	09-10-1995
		AU 669147 B	30-05-1996
		AU 3346693 A	19-07-1993
		BG 98863 A	31-05-1995
		EP 0618817 A	12-10-1994
		FI 942894 A	18-08-1994
		HU 68680 A	28-07-1995
		JP 7502430 T	16-03-1995
		NO 942330 A	17-08-1994
		NZ 246575 A	24-04-1997
		US 5824335 A	20-10-1998
		US 5520916 A	28-05-1996

WO 99/61080
PCT/EP99/03604

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

NOTARBARTOLO & GERVASI
MILANO
RECEIVED
13 DIC. 1999

Date of mailing (day/month/year) 02 December 1999 (02.12.99)	
Applicant's or agent's file reference 1931PTWO	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP99/03604	25 May 1999 (25.05.99)	27 May 1998 (27.05.98)

Applicant
FIDIA ADVANCED BIOPOLYMERS S.R.L. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 December 1999 (02.12.99) under No. WO 99/61080

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

NOTARBARTOLO & GERVASI
MILANO
RECEIVED
10 DIC. 1999

Date of mailing (day/month/year) 06 December 1999 (06.12.99)	
Applicant's or agent's file reference 1931PTWO P.F. Arch.	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP99/03604	25 May 1999 (25.05.99)	27 May 1998 (27.05.98)

Applicant
FIDIA ADVANCED BIOPOLYMERS S.R.L. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,
   ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,
   TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
A. Karkachi

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

REC'D 28 JUN 2000
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1931PTWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03604	25/05/1999	27/05/1998
International Patent Classification (IPC) or national classification and IPC A61L27/00		
Applicant FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/11/1999	26.06.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03604

I. Basis f th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

D scription, pages:

1-21 as originally filed

Claims, No.:

1-23 as received on 05/11/1999 with letter of 03/11/1999

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 13-23.

because:

☒ the said international application, or the said claims Nos. 13-23 (see separate sh et, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23 (see separate sheet, item 3)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23 (see separate sheet, item 3)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12 (see separate shet, item 2b); 13-23 (see separate sheet, it m 2a)
	No:	Claims	

2. Citations and explanations

see separate sheet

The following IPER is based on the assumption that the present application is fully entitled to its priority date as claimed.

1). Claims 13-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2). a). For the assessment of the present claims 13-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

b). The subject-matter of claims 1-12 fulfils the requirements of industrial applicability.

3). The most relevant prior art disclosure appears to be Example 30 of **D1** (=WO-A-93/11803) which mentions a non-woven fabric comprising a mixture of hyaluronic acid benzyl ester (HYAF 11) and a partial (75%) benzyl ester of hyaluronic acid (HYAF 11p75). However, the esterification degree of HYA mentioned in said example is higher than 85% (esterification degree 87,5%). Hence, the subject-matter of the present application is novel. As far as the applicant has demonstrated that the esterification degree for material A (see caim 1) is crucial to bone regeneration (see example 4, page 19 and figure 3) and the use of the materials B-E (see claim 1) for the preparation of the claimed biocompatible biomaterial has neither been disclosed nor rendered obvious in the available prior art, the subject-matter of the whole application is novel and involves also an inventive step.

4). Claims are misnumbered. Claim no.15 appears twice.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GERVASI, Gemma
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.06.00
Applicant's or agent's file reference 1931PTWO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03604	25/05/1999	27/05/1998

Applicant
FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Luck, E Tel.+49 89 2399-8238

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
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05/11/1999	26.06.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03604

I. Basis of the report

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

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☒ claims Nos. 13-23.

because:

☒ the said international application, or the said claims Nos. 13-23 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

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	No:	Claims	
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	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12 (see separate shet, item 2b); 13-23 (see separate sheet, item 2a)
	No:	Claims	

2. Citations and explanations

see separate sheet

The following IPER is based on the assumption that the present application is fully entitled to its priority date as claimed.

1). Claims 13-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2). a). For the assessment of the present claims 13-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

b). The subject-matter of claims 1-12 fulfils the requirements of industrial applicability.

3). The most relevant prior art disclosure appears to be Example 30 of **D1** (=WO-A-93/11803) which mentions a non-woven fabric comprising a mixture of hyaluronic acid benzyl ester (HYAF 11) and a partial (75%) benzyl ester of hyaluronic acid (HYAF 11p75). However, the esterification degree of HYA mentioned in said example is higher than 85% (esterification degree 87,5%). Hence, the subject-matter of the present application is novel. As far as the applicant has demonstrated that the esterification degree for material A (see caim 1) is crucial to bone regeneration (see example 4, page 19 and figure 3) and the use of the materials B-E (see claim 1) for the preparation of the claimed biocompatible biomaterial has neither been disclosed nor rendered obvious in the available prior art, the subject-matter of the whole application is novel and involves also an inventive step.

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CLAIMS

Use of at least one hyaluronic acid derivative selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) the sulphated derivatives or N-sulphated derivatives of hyaluronic acid,

said hyaluronic acid derivative being processed in the form of a three-dimensional structure enclosing empty spaces formed by communicating pores and/or fine fibres or microfibres entangled together for the preparation of a biocompatible biomaterial for the regeneration of mammal tissue, characterised in that:

i) said biocompatible biomaterial is free from cellular components and/or products thereof;

ii) when the hyaluronic acid derivative belongs to the aforementioned class (A) , and is processed in the form of a non woven tissue, it has an esterification degree lower than 85%

2. The use according to claim 1, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

3. The use according to claim 1, wherein said esterification degree is comprised between 40 and 85% .

4. The use according to anyone of claims 1, or 3, wherein said esterification degree is comprised between 45 and 75%.

5. The use according to anyone of claims 4-6, wherein said esterification degree is comprised between 60 and 70%,

6. The use according to anyone of claims 3-7 wherein said partial ester is the hyaluronic partial ester with benzyl alcohol.

7. The use according anyone of claims 1-2, wherein said hyaluronic acid derivative is an autocrosslinked ester of class (B).

8. The use according to claim 7 for osteochondral regeneration.

9. The use according to anyone of claims 1-8 wherein said biocompatible biomaterial consists essentially of at least one of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

10. The use according to anyone of claims 1-9 wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

11. The use according to anyone of claims 1-10, wherein said biocompatible biomaterial further contains pharmaceutically or biologically active substances.

12. The use according to any one of claims 1-11 wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.

13. A method for regenerating in vivo mammal tissue comprising applying in vivo to the site requiring such a treatment a biocompatible biomaterial containing at least one hyaluronic acid derivative selected from the group consisting of:

A) Esters of hyaluronic acid wherein part or all of the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series,

B) The autocrosslinked esters of hyaluronic acid wherein part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains,

C) The cross-linked esters of hyaluronic acid wherein part or all of the

carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating cross-linking by means of spacer chains ,

D) The hemiesters of succinic acid or heavy metal salts of the hemiester of succinic acid with hyaluronic acid or with partial or total esters of hyaluronic acid,

E) The sulphated derivatives or N-sulphated derivatives

said hyaluronic acid derivative being processed in the form of a three-dimensional structure enclosing hollow spaces formed by communicating pores and/or fine fibres or microfibres entangled together, wherein:

i) said biomaterial is free from cellular components and/or products thereof,

ii) when said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) and is processed in the form of non woven tissue, has an esterification degree lower than 85%

14. The method according to claim 13, wherein said mammal tissue is human tissue selected from the group consisting of epidermal, dermal, bone, cartilage, nerve, cardiovascular, adipose and hepatic tissues.

15. The method according to claim 13, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 40 and 85% and is processed in the form of non woven tissue.

15.The method according to claim 13, wherein said hyaluronic acid derivative is a partial ester of hyaluronic acid of class (A) having an esterification degree comprised between 45 and 75% and is processed in the form of non woven tissue.

16.The method according to claim 13, wherein said hyaluronic acid derivatives is a partial esters of hyaluronic acid of class (A) having an esterification degree comprised between 60 and 70% and is processed in the form of non woven tissue.

17.The method according to claim 13, wherein said partial ester is a hyaluronic partial ester with benzyl alcohol.

AMENDED SHEET

18.The method according to claim 13, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B).

19.The method according to claim 13, wherein said hyaluronic acid derivative is an autocrosslinked esters of class (B), for osteochondral regeneration.

20. The method according to claim 13, wherein said biocompatible biomaterial consists essentially of said hyaluronic acid derivatives in the form of three-dimensional structures with communicating hollow spaces created by pores and/or fine fibres or microfibres entangled together.

21. The method according to claim 13, wherein said biocompatible biomaterial further comprises at least another biocompatible natural, semisynthetic and/or synthetic polymer.

22.The method according to claim 13, wherein said biocompatible material further contains pharmaceutically or biologically active substances.

23.The method according to claim 13, wherein said biocompatible biomaterial further contains inside the non-woven fabrics, cords, liophylic compositions.

AMENDED SHEET

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP99/03604

International Filing Date (25.05.1999) 25 MAY 1999

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 1931PTWO

Box No. I TITLE OF INVENTION "BIOMATERIALS CONTAINING HYALURONIC ACID DERIVATIVES IN THE FORM OF THREE-DIMENSIONAL STRUCTURES FREE FROM CELLULAR COMPONENTS OR ....

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FIDIA ADVANCED BIOPOLYMERS S.R.L.
Via De' Carpentieri 3
72100 BRINDISI
ITALY

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PAVESIO Alessandra
Via Decorati al Valore Civile 159
35100 PADOVA
ITALY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GERVASI Gemma
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria 9
20122 MILANO
ITALY

Telephone No. 02.5417991

Facsimile No. 02.54179920

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DONA' Massimo
Via IV Novembre 106
35020 DUE CARRARE (Province of PADOVA)
ITALY

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CALLEGARO Lanfranco
Via Monte Grappa 6
36016 THIENE (Province of VICENZA)
ITALY

This person is:
- ☐ applicant only
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Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AL** Albania
- [X] **AM** Armenia
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- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina
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- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China
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- [X] **CZ** Czech Republic
- [X] **DE** Germany
- [X] **DK** Denmark
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- [X] **IS** Iceland
- [X] **JP** Japan
- [X] **KE** Kenya
- [X] **KG** Kyrgyzstan
- [X] **KP** Democratic People's Republic of Korea .....
- [X] **KR** Republic of Korea
- [X] **KZ** Kazakhstan
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MD** Republic of Moldova
- [X] **MG** Madagascar
- [X] **MK** The former Yugoslav Republic of Macedonia .....
- [X] **MN** Mongolia
- [X] **MW** Malawi
- [X] **MX** Mexico
- [X] **NO** Norway
- [X] **NZ** New Zealand
- [X] **PL** Poland
- [X] **PT** Portugal
- [X] **RO** Romania
- [X] **RU** Russian Federation
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia
- [X] **SK** Slovakia
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan
- [X] **TM** Turkmenistan
- [X] **TR** Turkey
- [X] **TT** Trinidad and Tobago
- [X] **UA** Ukraine
- [X] **UG** Uganda
- [X] **US** United States of America .....
- [X] **UZ** Uzbekistan
- [X] **VN** Viet Nam
- [X] **YU** Yugoslavia
- [X] **ZW** Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] **AE** United Arab Emirates .....
- [X] **ZA** South Africa .....
- [ ] .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all ther designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that th se additional designati ns are subject to c nfirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 27 MAY 98 (27. 05. 1998)	PD98A000131	IT ~~ALY~~		
item (2) 21 DEC 98 (21. 12. 1998)	PD98A000299	IT ~~ALY~~		
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	: 4
description (excluding sequence listing part)	: 21
claims	: 4
abstract	: 1
drawings	: 3
sequence listing part of description	:
Total number of sheets	: 33

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☒ separate signed power of attorney 2 forms
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: - accompanying letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Milano, 20.5.1999

Gemma Gervasi

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1. Date of actual receipt of the purported international application: (25. 05. 99) 25 MAY 1999
2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

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